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Maximising BOLD sensitivity through automated EPI protocol optimisation

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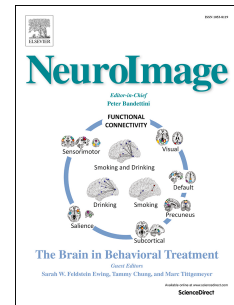
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1 Title:

2 Maximising BOLD Sensitivity through Automated EPI Protocol Optimisation

3

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23 Highlights:

- 24 • Significant BOLD sensitivity increase by optimization of z-shim, gradient polarity
25 and slice tilt

- 1 • Method based on numerical signal simulations informed by large database of
- 2 magnetic field maps
- 3 • saves time and expensive measurements
- 4 • automated and flexible optimization of multiple EPI parameter settings

6 **Abstract:**

7 Gradient echo echo-planar imaging (GE EPI) is used for most fMRI studies but can suffer
8 substantially from image distortions and BOLD sensitivity (BS) loss due to susceptibility-
9 induced magnetic field inhomogeneities. While there are various post-processing methods for
10 correcting image distortions, signal dropouts cannot be recovered and therefore need to be
11 addressed at the data acquisition stage. Common approaches for reducing susceptibility-
12 related BS loss in selected brain areas are: z-shimming, inverting the phase encoding (PE)
13 gradient polarity, optimizing the slice tilt and increasing spatial resolution. The optimization
14 of these parameters can be based on atlases derived from multiple echo-planar imaging (EPI)
15 acquisitions. However, this requires resource and time, which imposes a practical limitation
16 on the range over which parameters can be optimised meaning that the chosen settings may
17 still be sub-optimal. To address this issue, we have developed an automated method that can
18 be used to optimize across a large parameter space. It is based on numerical signal
19 simulations of the BS loss predicted by physical models informed by a large database of
20 magnetic field (B_0) maps acquired on a broad cohort of participants. The advantage of our
21 simulation-based approach compared to previous methods is that it saves time and expensive
22 measurements and allows for optimizing EPI protocols by incorporating a broad range of
23 factors, including different resolutions, echo times or slice orientations. To verify the
24 numerical optimisation, results are compared to those from an earlier study and to
25 experimental BS measurements carried out in six healthy volunteers.

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Introduction:

Gradient echo echo-planar imaging (GE EPI) (Mansfield, 1977) is used for most functional magnetic resonance imaging (fMRI) studies due to its high acquisition speed and its sensitivity to the blood oxygenation level-dependent (BOLD) effect (Ogawa et al., 1990).

However, EPI quality can suffer substantially from image distortions and BOLD sensitivity loss (BS) caused mainly by magnetic field inhomogeneities. These inhomogeneities originate from differences in the magnetic susceptibility between tissue and air and are especially prominent in the orbitofrontal cortex (OFC), the medial temporal and the inferior temporal lobes (Ojemann et al., 1997, Devlin et al., 2000, Lipschutz et al., 2001).

The correction of image distortions is mostly performed during image post-processing and there exist various methods (Andersson et al., 2001, Bowtell et al., 1994, Hutton et al., 2002, Jezzard and Ballaban, 1995, Sutton et al., 2004, Weiskopf et al., 2005, Zaitsev et al., 2004, Mohammadi et al., 2010). However, the loss of BS still remains and needs to be addressed at the data acquisition stage.

For reducing susceptibility-related signal losses a variety of techniques have been introduced. For example, the differences in susceptibility can be reduced directly by placing diamagnetic materials with susceptibilities similar to tissue around the participant (Fritzsche et al., 1995) or using oral shim coils (Hsu and Glover, 2005, Wilson and Jezzard, 2003). However, such shimming is limited to a relatively small area and situations with strong susceptibility gradients. Furthermore, additional hardware and increased manual effort are needed, potentially also causing additional inconvenience to the patient or volunteer. Alternatively, susceptibility-induced signal losses can be reduced by the use of 3D tailored radiofrequency (RF) pulses (Stenger et al., 2000, Yip et al., 2006, Zheng et al., 2013) or spectral-spatial

1 pulses (Anderson et al., 2014, Yip et al., 2009) without the need for additional hardware.
2 However the design of these pulses is computationally expensive and leads to prolonged RF
3 pulse durations, hence echo time TE and repetition time TR, and often reduce signal-to-noise-
4 ratio (SNR) in well-shimmed areas (Cho and Ro, 1992).

5 Various strategies have been developed for compensating susceptibility-induced gradients in
6 selected brain areas. The z-shimming approach (Frahm et al., 1988, Ordidge et al., 1994,
7 Posse et al., 1999, Deichmann et al., 2003, Rick et al., 2010) compensates gradients in the
8 slice direction. This has been extended to in-plane gradients in the phase-encoding (PE)
9 direction (Deichmann et al., 2003, De Panfilis and Schwarzbauer, 2005) and to the readout
10 (RO) direction (Weiskopf et al., 2007). One drawback of adding compensation gradients to
11 the sequence however is the reduction of spatial and temporal resolution. Other approaches
12 that avoid prolonging the acquisition significantly are optimising the slice tilt (De Panfilis
13 and Schwarzbauer, 2005, Weiskopf et al., 2006) and TE (Domsch et al., 2013, Stöcker et al.,
14 2006). Signal dropouts can also be improved by multi-echo summation (Posse et al., 1999),
15 increasing the spatial resolution (Robinson et al., 2004, Weiskopf et al., 2007), using thin
16 slices (Frahm et al., 1993, Merboldt et al., 2000) or combining high resolution with high
17 acquisition speed by parallel imaging (Heidemann et al., 2012, Domsch et al., 2015). The
18 poor temporal resolution of high resolution acquisition techniques can additionally be
19 improved by multiband EPI sequences (Nunes et al., 2006, Setsompop et al., 2012) shown to
20 improve signal dropouts in (Kim et al., 2016).

21 The optimisation of all these parameters can be based on atlases derived empirically from
22 multiple EPI acquisitions (Weiskopf et al., 2006). This however is resource and time
23 consuming. Thus, atlases reporting voxel-wise optimal sequence parameters cover a limited
24 set of parameters, e.g. z-shim, the gradient polarity and the slice tilt, over a relatively coarse

1 range and with a particular acquisition protocol, e.g. oblique transverse EPI acquisition at
2 3mm resolution only (Weiskopf et al., 2006).

3 In the present work we develop and employ a flexible and automated BS optimization
4 method that is based on the prediction of BS loss using the physical models accounting for
5 through-plane dephasing and local echo time/k-space shifts and signal loss due to
6 susceptibility-induced in-plane gradients in the PE (Deichmann et al., 2003, De Panfilis and
7 Schwarzbauer, 2005) and RO direction (Weiskopf et al., 2007). A database of magnetic (B_0)
8 field maps acquired over a large population of 138 volunteers serves as input for the
9 calculations. Unlike the previous experimental approaches, the presented approach allows
10 arbitrary 2D-EPI acquisition protocols, including varying resolution, echo time or slice
11 orientation, to be optimised making it more easily and widely applicable.

12

13

14 **Methods:**

15 *BS calculation*

16 The BS is defined as the local signal intensity change due to a local change of the effective
17 transverse relaxation time T_2^* being altered during neuronal activation. Given the local echo
18 time TE and the signal intensity I, it can be calculated according to (Lipschutz et al., 2001):

$$19 \quad BS = TE \cdot I \quad (1)$$

20 In the following I_0' denotes the initial signal intensity at TE=0 and TE_0 and I_0 denote the
21 respective echo time and initial signal intensity if there are no susceptibility gradients.

22 The signal intensity I of a gradient echo EPI sequence is given by:

$$23 \quad I = I_0' \cdot \exp\left(-\frac{TE}{T_2^*}\right) \quad (2)$$

24 A susceptibility gradient in the slice direction G_S^{susc} causes through-plane spin dephasing and
25 thus a signal loss. It can be compensated with a z-shim gradient G_S^{shim} (Frahm et al., 1988,

1 Ordidge et al., 1994, Deichmann et al., 2003, Rick et al., 2010) applied with opposite polarity
 2 in the slice direction for a time period τ . For a Gaussian-shaped excitation profile and a slice
 3 thickness of Δz , the corresponding image intensity is given according to (Deichmann et al.,
 4 2002) by:

$$5 \quad I = I_0 \cdot \exp(-\Psi^2), \text{ with } \Psi = \gamma \cdot \frac{\Delta z}{4\sqrt{\ln(2)}} \cdot (G_S^{susc} \cdot TE + G_S^{shim} \cdot \tau) \quad (3)$$

6 γ is the gyromagnetic ratio. Susceptibility gradients along in-plane directions sum up with the
 7 imaging gradients causing distortion of the data in k-space. A susceptibility gradient in the PE
 8 direction G_P^{susc} causes a change of the local TE and the modified initial signal intensity I'
 9 (Deichmann et al., 2002) according to:

$$10 \quad TE = \frac{TE_0}{Q}, I' = \frac{I_0'}{Q}, \text{ with } Q_{\pm} = 1 \mp \frac{\gamma \cdot \Delta t}{2\pi} \cdot FoV_P \cdot G_P^{susc} \quad (4)$$

11 FoV_P is the field of view in phase encoding direction and Δt the inter-echo spacing during the
 12 EPI readout. The sign in the subscript of Q refers to the PE gradient polarity of the EPI
 13 readout and, as referred to later, is defined by the polarity of the PE prewinder moment used
 14 in the EPI sequence. A positive PE gradient polarity corresponds to a positive PE prewinder
 15 moment (and thus negative phase blip gradients) thus pointing from the posterior to the
 16 anterior part of the brain in the example of the transverse acquisition.

17 Equations (1) - (4) combine to:

$$18 \quad BS = \frac{BS_0}{Q^2} \cdot \exp\left(-\frac{TE-TE_0}{T_2^*}\right) \cdot \exp(-\Psi^2) \quad (5)$$

19 Both in-plane susceptibility gradients in PE direction and in RO direction can shift the centre
 20 of k-space outside the acquisition window and therefore cause a complete signal dropout. For
 21 susceptibility gradients in the PE direction, in the case of symmetric k-space sampling with
 22 sampling duration TA of the EPI readout, the following condition has to be fulfilled
 23 (Deichmann et al., 2003) to prevent signal dropout:

$$24 \quad TE_0 - \frac{TA}{2} \leq TE \leq TE_0 + \frac{TA}{2} \quad (6)$$

1 For a susceptibility gradient in the RO direction G_R^{susc} in order for the k-space shift ΔK_{susc} not
 2 to exceed the acquisition window in the RO direction the following condition has to be
 3 fulfilled if Δx is the RO resolution (Weiskopf et al., 2007):

$$4 \quad |\Delta K_{\text{susc}}| = |\gamma \cdot TE \cdot G_R^{\text{susc}}| \leq \frac{\pi}{\Delta x} \quad (7)$$

5 If one of the conditions (6) or (7) is not fulfilled, this results in a complete signal loss and
 6 BS=0.

7

8 *Acquisition of a large magnetic field map database*

9 The BS simulations rely on accurate estimates of the typical static magnetic field distribution
 10 in the brain. B_0 field maps from 138 healthy volunteers (49 men, age range 19 to 75 years,
 11 age mean \pm standard deviation 46.6 \pm 21 years), who were scanned as part of the neuroscience
 12 research program at our imaging centre (Wellcome Centre for Human Neuroimaging;
 13 WCHN) with Ethics approval, served as an estimate for a population of healthy volunteers.
 14 The field maps were acquired using a double echo FLASH sequence with the following
 15 parameters: 64 transverse slices, slice thickness=2 mm, gap between slices=1 mm, TR=1020
 16 ms, $\alpha=90^\circ$, short TE=10 ms, long TE=12.46 ms, BW=260 Hz/pixel, PE direction right-left,
 17 FOV=192 \times 192 mm², matrix size 64 \times 64, flow compensation. In addition to the field maps,
 18 anatomical data (3D FLASH) were recorded for each volunteer as part of a whole brain
 19 quantitative multi-parameter mapping (MPM) protocol (Callaghan et al., 2014). All data were
 20 acquired on a 3 Tesla whole body MR scanner (Magnetom TIM TRIO, Siemens Medical
 21 Solutions, Erlangen, Germany) using the standard 32 channel head coil for RF receive and
 22 the RF body coil for transmission. Informed written consent was obtained from each
 23 volunteer prior to scanning.

24

25 *Data pre-processing and BS calculation*

1 All data were analysed and processed with Matlab (MathWorks, Natick, MA) and SPM8
2 (<http://www.fil.ion.ucl.ac.uk/spm>) and custom-written Matlab programs. Field maps were
3 estimated from the GE data using the Field Map toolbox (Hutton et al., 2002). Field gradients
4 were derived from the field maps by numerical differentiation and normalised to MNI space
5 using the individual anatomical data using Dartel (Ashburner 2007). No modulation and
6 smoothing were applied to preserve the values. After normalization they were averaged.
7 Based on this, BS maps were calculated according to Equation (5). Additionally, BS maps
8 were calculated for each subject separately, providing an estimate of the variability of BS
9 changes and optimal parameters across the population.

10

11 *Optimization of BS*

12 The optimization was carried out by stepping through all parameters within the ranges as
13 described further down to find the EPI parameters maximizing the BS. This optimisation was
14 carried out first voxel-wise across the whole brain. Then, separate optimisations were done
15 for the following regions of interest (ROIs) by maximizing the mean BS across the respective
16 ROIs: (1) medial orbitofrontal cortex (mOFC) and rostral–ventral anterior cingulate cortex
17 (rACC), (2) inferior temporal lobes, (3) temporal poles, (4) amygdala and (5) hippocampus
18 and para-hippocampus. The ROIs were based on the automated anatomical labeling toolbox
19 (Tzourio-Mazoyer et al., 2002) and were constructed to compare with previous work as
20 described in detail in (Weiskopf et al., 2006). Optimized EPI parameter sets were only
21 accepted if the BS loss in areas not affected by susceptibility related gradients, i.e. for a
22 susceptibility gradient with zero value, did not exceed 15% (Weiskopf et al., 2006) compared
23 to the standard EPI. Otherwise, the EPI parameter set with the next highest BS not exceeding
24 the 15% BS loss was chosen. In other words, the 15% cut off served as a hard boundary
25 condition for the optimization.

1 While the simulations can be carried out for arbitrary 2D-EPI protocols, for conciseness we
2 determined the optimal PE polarity, slice angulation and in-plane rotation and through plane
3 z-shim gradients for the following reference EPI protocols with settings typical of studies
4 carried out at the WCHN. Since particular slice orientations impose different restrictions on
5 the spatial coverage that can be achieved, the three primary planes (transverse, sagittal,
6 coronal) were investigated separately. The reference protocols are:

7 **(I) Standard resolution protocol:** TE=30ms, echo spacing=0.5ms, in-plane
8 resolution=3x3mm², slice thickness=3mm, matrix size=64x64, no acceleration by parallel
9 imaging or partial Fourier each for transverse, sagittal and coronal slices respectively with PE
10 gradient directions pointing from anterior to posterior for transverse and sagittal slices and
11 feet to head for coronal slices.

12 **(II) High-resolution protocol:** TE=30ms, echo spacing=0.78ms, in-plane
13 resolution=2x2mm², slice thickness=2mm, matrix size=96x96, no acceleration by parallel
14 imaging or partial Fourier again for transverse, sagittal and coronal slices respectively with
15 PE gradient directions pointing from anterior to posterior for transverse and sagittal slices and
16 feet to head for coronal slices.

17 **(III) Accelerated high-resolution protocol:** This protocol was identical to (II) but a
18 speedup using GRAPPA with factor 2 in the PE direction was simulated.

19 The ranges used for each of the parameters to be optimised were: positive or negative polarity
20 of the PE gradient, slice tilt ranging from -45° to 45° in steps of 5°, and z-shim gradient
21 pointing in slice direction with a moment ranging from -5 to 5mT/m*ms in steps of
22 0.5mT/m*ms.

23 Figure 1 illustrates the definitions of the coordinate systems for the different main slice
24 orientations and the corresponding directions for slice angulations and in-plane rotations,
25 respectively. For example, in case of the transverse acquisition a slice angulation means a

1 rotation around the RO axis which is pointing from the right to the left hemisphere of the
2 brain with a positive rotation angle denoting an angulation of the anterior part of the slices
3 from head to feet.

4

5 *Validation by comparison to published approaches*

6 The simulation results were compared to results obtained from measured data reported in
7 (Weiskopf et al., 2006). A BS optimization was performed with the same fixed sequence
8 parameters and parameter range for the simulation as used in the measurements at 3T. The
9 following fixed EPI imaging parameters were used: TE=30ms, slice thickness=2mm, in-plane
10 resolution=3x3mm², echo spacing=0.33ms, matrix size=64x64, transverse slices and the PE
11 gradient directions pointing from anterior to posterior. The following parameters were
12 optimized for the ROIs listed above and varied in the same range as in the publication: slice
13 tilt ranging from -45° to 45° in steps of 15°, z-shim gradient pointing in slice direction with a
14 moment ranging from -4 to 4mT/m*ms in steps of 1mT/m*ms and the polarity of the PE
15 gradient pointing either in positive or negative direction.

16

17 *Validation by comparison to in vivo data*

18 The simulation output was compared to experimental data from in vivo measurements. Six
19 volunteers (four male, age range 27 to 38 years, age mean±sd = 33±4 years) were scanned
20 with various slice tilts, z-shims, PE gradient polarity and slice orientation on a 3T Tim Trio
21 MRI scanner. The parameters of the EPI protocol were fixed to match reference protocol (1)
22 above. The other parameters were: 48 slices, TR=3360ms and 13% phase oversampling
23 (acquired k-space lines=64x74). A B₀ field map (as described above for the database creation)
24 was acquired for distortion correction of the EPI images and for simulating the BS and a short
25 anatomical scan (3D MP-RAGE sequence with 1mm isotropic resolution, field-of-view =

1 176x224x256 mm³ and TI/ α /TE/TR = 900ms/9°/2.26ms/1900ms) were also acquired.
2 Informed written consent was obtained from each volunteer before participating and the study
3 was approved by the local Ethics committee.
4 Data were acquired using a circularly polarized (CP) head coil for RF receive and
5 transmission in order to facilitate reconstruction of robust magnitude and phase data avoiding
6 multi-channel image reconstruction.
7 The measurement was repeated 36 times with different combinations of main slice
8 orientations (transverse and sagittal), slice tilts/in plane rotations (-30, 0 and 30°), z-shim
9 (through plane) gradient moments (-3, 0 and 3mT/m*ms) and PE gradients with a positive
10 and negative polarity. For each measurement, 6 volumes were acquired, and both magnitude
11 and phase images were exported for later evaluation.
12 For each EPI acquisition and each volunteer, experimental BS maps were calculated from the
13 complex image data using the method described in appendix C of Deichmann et al., 2002 for
14 determining the local TE via the phase difference between two adjacent points in the PE
15 direction. The BS was then calculated as the product of this local TE and the magnitude of
16 the image intensity I: BS=TE*I. These BS maps were undistorted using the Field Map
17 toolbox (Hutton et al., 2002). BS gain maps, in percent units, were calculated voxel-wise
18 according to $BS_{\text{gain,exp}} = 200*(BS-BS_{\text{ref}})/(BS + BS_{\text{ref}})$ using the default protocol, i.e. with no
19 slice tilt, zero z-shim gradients and a positive polarity of the PE gradient as reference BS_{ref} .
20 For comparison, the BS was simulated for each EPI protocol and each volunteer, using the
21 individual's specific field map. Similar to the calculation above expected BS gain maps, in
22 percent units, were calculated according to $BS_{\text{gain,sim}} = 200*(BS-BS_{\text{ref}})/(BS + BS_{\text{ref}})$ from the
23 simulation using the default protocol, i.e. with no slice tilt, zero z-shim gradient and a
24 positive polarity of the PE gradient as reference BS_{ref} .

1 In order to compare the simulated and experimental BS gain only within the brain, a brain
2 mask was obtained by segmenting the MP-RAGE scan, summing the WM, GM and CSF
3 tissue probabilities and thresholding at 0.95. Each of the simulated BS maps calculated for
4 each individual were co-registered to the experimental EPI data acquired with the default
5 protocol and then the difference between the simulated and experimental BS gain
6 $BS_{diff} = BS_{gain, sim} - BS_{gain, exp}$ was calculated. Mean and standard deviation of the BS gain
7 difference were evaluated within the brain mask.

8
9

10 **Results**

11 *Field gradients in 138 volunteers*

12 Figure 2 shows maps of the magnetic field gradients along the X-direction (left-right, top
13 row), Y-direction (posterior-anterior, middle row) and Z-direction (head-feet, bottom row).
14 Maximum gradients, of up to $\pm 100 \mu\text{T/m}$ were found in the temporal and orbitofrontal areas.
15 While the contribution of gradients in Y- and Z-direction were found to be left-right
16 symmetric, an antisymmetric (same magnitude, but opposite sign) contribution of gradients in
17 X-direction was seen. Field gradients in Y-direction with opposing signs close to each other
18 were observed in the orbitofrontal and temporal areas.

19 *Results for Optimization of BS*

20 Figure 3 shows maps of the voxel-wise optimized parameters for the case of the *standard*
21 *resolution protocol I* with a transverse slice orientation. Shown are, from top to bottom, maps
22 of the optimal z-shim gradient moment (a), the optimal slice angulation (b) and the maximum
23 BS gain with the optimal z-shim gradient and slice angulation compared to the standard EPI
24 protocol with no shim gradient or slice angulation (c). The results are shown for both a
25 positive PE gradient (top row) and a negative PE gradient (bottom row) respectively.

1 Similarly, figures 4 and 5 show the optimized maps for the *standard resolution protocol I*
2 acquisitions with sagittal and coronal orientation respectively.

3 For the optimal z-shim gradient, a negative gradient moment was found to yield the highest
4 BS in the orbitofrontal cortex and a positive gradient moment in the temporal lobes in case of
5 the transverse acquisition (figure 3a) as previously reported for the measurements with a
6 negative PE gradient. For the sagittal acquisition, a left-right antisymmetric distribution of z-
7 shim gradient moments was found in the orbitofrontal cortex and the temporal lobe (figure
8 4a). Combined with the findings in the BS gain the symmetry and antisymmetry can be
9 explained by the susceptibility-induced field inhomogeneities that mainly point
10 symmetrically along the head-feet direction and antisymmetrically in the left-right direction
11 near these areas (figure 2). For the coronal acquisition, areas with positive and negative z-
12 shim gradients were found close to each other in the orbitofrontal cortex and the temporal
13 lobe (figure 5a).

14 For the optimal slice angulations/in-plane rotations the optimization results in positive values
15 for transverse/sagittal acquisition in the orbitofrontal cortex and negative values in the
16 temporal lobes. Like for the optimized z-shim gradient moments, areas with positive and
17 negative slice angulations could be found close to each other in the orbitofrontal cortex and
18 temporal lobes in the coronal acquisition case. The similar values for slice angulations and
19 rotations for transverse and sagittal acquisitions are driven by the same PE direction for both
20 acquisitions. Similar to the results for the z-shim gradients, areas with positive and negative
21 values for the slice angulations were found close to each other in the orbitofrontal cortex and
22 the temporal lobe in case of the coronal acquisition (figure 5b) according to the field gradient
23 distribution with opposite signs close to each other in the posterior-anterior direction (figure
24 2).

1 The results of the optimization based on different ROIs (mOFC and rACC, inferior temporal
2 lobes, temporal poles, amygdala and Hippocampus and Parahippocampus), listed in table 1,
3 reflect the findings presented in figures 3-5: positive shim gradients in the temporal lobes but
4 negative in the orbitofrontal cortex in the case of the transverse acquisition in the PE neg
5 scheme. Z-shim values near zero were found for the same regions for the sagittal and coronal
6 acquisitions reflecting the symmetry and antisymmetry of the field inhomogeneities and
7 opposing values for the shim gradients close to each other within these areas.

8 Figures 6-8 provide more details for the ROI optimization in addition to table 1 by showing
9 the BS gain distribution depending on the optimized parameters. Two types of optimization
10 were performed: one based on the group-average fieldmap and the other one based on
11 individual subject fieldmaps. The BS gain for each ROI (columns from left to right) of table 1
12 is shown for all combinations of slice tilt and z-shim in the colour maps assuming either a
13 negative PE direction (a) or a positive phase encoding direction (b). Similarly, for each ROI
14 the frequency of the optimal parameters slice tilt and z-shim is shown in the histograms (c)
15 and (d) respectively in case of the optimization based on the individual field maps. In case of
16 (c) the number of simulations resulting in a given optimized slice tilt is displayed for each PE
17 direction separately. This representation was chosen since an opposite PE direction also
18 results in optimized slice tilts with opposite sign. In (d) the number of simulations resulting in
19 a given optimized z-shim value is displayed for both PE directions combined. In addition, the
20 impact of an optimization for each single ROI on the BS of all other ROIs is shown in the
21 coloured checkerboard in e). Figures 6-8 show the results for the optimization of the
22 transverse, sagittal, and coronal standard resolution protocol respectively.

23 In case of the optimization of the transverse protocol a clear bimodal contribution of BS
24 depending on the slice tilt can be observed for both PE directions with a strong preference for
25 the maximum slice tilt (figure 6a-b): a change of the PE direction results in an opposite sign

1 of the optimal slice tilt. The subject by subject analysis in figure 6c) shows that especially for
2 the Temporal Lobes and the Amygdala there was no clear preference for the negative PE with
3 -45° slice tilt or the positive PE with 45° slice tilt parameter set. The contribution of optimal
4 z-shim values is rather sharp with almost all subjects within an interval of ± 0.5 mT/m*ms
5 around the maximum (figure 6d). The effect of optimizing a protocol for one ROI on other
6 ROIs (figure 6e) shows that optimizing the OFC results in a reduction of the BS in all other
7 ROIs, especially in the Amygdala (BS loss of 26%), while the optimization of all other ROIs
8 also increases the BS of all ROIs except for the OFC. The optimization of the Amygdala in
9 turn yields a rather strong BS loss of 21% in the OFC. Additionally, the strong z-shim
10 gradient suggested for the Amygdala, results in a reduced BS of the well shimmed areas and
11 therefore for the whole brain (BS losses 8% and 12% respectively).

12 Due to the same PE direction for both transverse and sagittal acquisition the results for the
13 optimization of the sagittal protocol shown in figure 7 in terms of slice tilt and PE direction
14 are similar to figure 6. However, due to the antisymmetric distribution of susceptibility-
15 induced field inhomogeneities in the left-right direction, the optimal z-shim values are
16 centered around zero.

17 In case of the optimization of the coronal protocol (figure 8), a clear preference for one PE
18 direction (negative for OFC and positive for all other ROIs) with a rather broad distribution
19 of optimal slice tilts can be seen in contrast to transverse orientation. While the optimal z-
20 shim values were centred sharply about zero in the subject by subject analysis, it became a
21 function of slice tilt in the simulated parameter space, especially in the Temporal Lobes and
22 Amygdala.

23 The results of the optimization in different ROIs for different resolutions (3mm and 2mm
24 isotropic) and using GRAPPA, factor 2 with 2mm isotropic resolution for oblique transverse
25 acquisition are listed in table 2 and show comparable results for the optimized parameters z-

1 shim, slice angulation and PE gradient polarity. The respective BS gains are higher for the
2 2mm isotropic compared to the 3mm isotropic resolution probably due to the fact that with a
3 higher in-plane resolution, and thus a longer acquisition time, the susceptibility gradients in
4 the PE direction result in greater BS losses potentially being compensated by the use of the
5 optimal parameters. The BS gain using GRAPPA, factor 2 is lower compared to using no
6 GRAPPA. This is probably due to less signal losses from susceptibility gradients in PE
7 direction due to the shorter acquisition window.

8 *Validation by comparison to published approaches*

9 A comparison of optimal parameters determined for different ROIs resulting from the
10 simulations and by doing the optimization with multiple EPI acquisitions according to
11 (Weiskopf et al., 2006) are shown in table 3. The parameter optimization resulted in values of
12 the z-shim, slice angulation and PE gradient polarity being in good agreement for the mOFC
13 and rACC, inferior temporal lobes, temporal poles and the amygdala. However, for the
14 hippocampus the tilt pointed in the opposite direction as did the PE gradient polarity. This can
15 be explained with similar BS gains for parameter sets with opposing slice tilts and PE
16 gradient polarity respectively for the hippocampus region.

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18 *Validation by comparison to in vivo data*

19 The comparison between simulated and experimental BS gains showed good agreement for
20 each of the 36 protocols investigated (figure 9). Deviations were typically around 5% and did
21 not exceed 10%, which is within the standard deviation across the brain mask, which ranges
22 from 10-20%. Histograms of the deviations pooled over the brain mask and all subjects
23 showed a Gaussian distribution, suggesting that deviations were largely driven by noise
24 rather than systematic bias due to poor BS model performance.

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Discussion

In this study we presented a flexible and automated BS optimization method based on numerical simulations of the BS loss using physical models that account for the effects of susceptibility-induced gradients in the through-plane (Deichmann et al., 2003), phase-encoding (Deichmann et al., 2003, De Panfilis and Schwarzbauer, 2005) and readout direction (Weiskopf et al., 2007) and informed by a database of magnetic (B₀) field maps over a large population of 138 volunteers. The simulations produced results that are in good agreement with earlier experimental optimization outcomes (Weiskopf et al., 2006) and the predicted BS increases are in line with the experimental measures of BS in six volunteers.

Previous optimizations have been based on atlases derived from multiple EPI acquisitions making them resource and time consuming. Consequently, they were performed only for a limited number of parameters over a restricted range and by acquiring data from a small number of volunteers only, e.g. optimizing the z-shim, the gradient polarity and the slice tilt for oblique transverse slices and a resolution of 3mm on five volunteers only (Weiskopf et al., 2006). Results from these experimental studies suggested, for example, the use of a strong positive slice angulation in temporal regions but a strong negative angulation in orbitofrontal regions, i.e., tilting the slice downwards or upwards at the front (see Fig. 1 for definition of slice angles). These results are confirmed by our simulations when considering the case of oblique transverse slices as used in the original experimental investigation. Extending the optimization to coronal slices, shows that for some regions like the temporal poles coronal slices would be the better choice with respect to BS.

The advantage of the proposed method is that the optimization of parameters is done by simulations thus avoiding time and resource consuming measurements. This also allows for

1 the optimization to be performed over a larger parameter space including varying resolution,
2 echo time or slice orientation. The parameters that are optimized and the range of
3 optimization can easily be adapted without the need for additional measurements. In addition,
4 various boundary conditions can be readily implemented in the optimization (e.g. preferred
5 slice tilts for specific anatomical coverage). Although here the optimization yielded a single
6 set of parameters (slice angulation, z-shim and PE direction) to be applied for all slices,
7 optimized parameters could in principle be varied from slice to slice, e.g. allowing for slice
8 dependent TE (Domsch et al., 2013) and z-shim (Rick et al., 2010, Bonnici et al., 2012,
9 Finsterbusch et al., 2012). Our results indicate that such an approach would be of benefit in
10 regions such as the temporal lobes where both positive and negative susceptibility gradients
11 are in close spatial proximity requiring opposing optimal parameter settings to maximise BS.
12 Especially in case of coronal or sagittal acquisitions we found a left-right antisymmetric
13 distribution of the field inhomogeneities and correspondingly opposing values for the optimal
14 shim gradients (figures 2 and 3). This results in near zero z-shim values for the ROI
15 optimisation (table 1) in case of one optimal parameter set valid for all slices and ROIs with
16 voxels being distributed symmetrically on the left and right hemisphere of the brain. In this
17 case slice-specific z-shims could yield better results if available.

18 Although coronal slices may yield a higher BS in temporal areas, the slice orientation affects
19 the brain coverage that can be achieved with a specific TR and slice thickness as well.
20 Coronal slices compared to transverse slices have the disadvantage of a lower brain coverage
21 at the same TR and require a longer TR if whole brain coverage is needed, i.e. an increase in
22 scan time of about 30-35 % (Mennes et al., 2014). Similarly, the slice thickness affects the
23 number of slices necessary to cover a specific region and hence the needed TR and hence
24 limit the parameter range or prescribe specific parameters if necessary. Therefore, a
25 compromise has to be found and the user must decide on the necessary coverage and

1 maximum TR. For example, the study of the amygdala typically requires high spatial and
2 temporal resolution as well as extended coverage in order to account for its small dimensions
3 while concurrently allowing its activation to be interpreted within a complex network of brain
4 regions (Stöcker et al., 2006).

5 The use of the slice tilt can also be limited by the gradient performance, since gradients in
6 different directions contribute differently to peripheral nerve stimulations. Also when
7 applying gradients in different directions with respect to the slices at the same time, the real
8 gradients played out on the scanner can be higher due to vectorial summation and gradient
9 amplitudes as well as slew rates may exceed hardware specifications, if already the reference
10 protocol was near the limit. This means that either a reduced gradient performance with a
11 reduced temporal resolution has to be accepted, to ensure the setup of the optimized protocol
12 at the scanner, or the range of possible parameter settings has to be limited for the simulation
13 and optimization. Also, in case of extreme magnetic field variations as in the vicinity of
14 metallic implants, the proposed approach is likely to underperform or fail due to induction of
15 eddy currents, requirement of excessive z-shim gradient moments or issues with the RF
16 excitation.

17 Additionally, the simulation only optimizes the BS. Temporal SNR or potential artefacts have
18 to be additionally taken into account when defining the parameter space for optimization. For
19 example, parallel imaging on the one hand increases the acquisition speed allowing for a
20 lower TR, important e.g. for high resolution imaging of the whole brain. A short TR can also
21 be used to reduce physiological noise by removal of high frequency noise originating from
22 respiration and cardiac pulsation (Todd et al., 2017). On the other hand it reduces the overall
23 SNR and poses a potential source of artifacts arising from g-factor penalties and issues with
24 reference scans in combination with volunteer movement (Feinberg and Setsompop, 2013).
25 New imaging techniques like simultaneous multislice imaging offer the possibility of

1 accelerating the imaging without direct loss of SNR. However, still SNR loss occurs due to
2 unfavourable g-factors and slice leakage artefacts occur in combination with in-plane
3 acceleration making the overall statistical benefit dependant on the used hardware and region
4 of interest and requiring a careful consideration for choosing the best acceleration factor
5 (Todd et al., 2016).

6 The optimization of an EPI protocol for a specific region often comes with the reduction of
7 the BS in other regions. In this study the BS loss in areas not affected by susceptibility related
8 gradients, i.e., well shimmed areas, was limited to 15%. However, the BS loss may be
9 significantly higher in areas requiring different optimal parameters due to susceptibility
10 induced field gradients pointing in opposite direction compared to the optimized areas
11 (Weiskopf et al., 2006). While the TE or z-shim could be optimized slice-wise, provided that
12 appropriate sequences are available, the slice tilt can be optimized only for a single or
13 combined ROI.

14 The field maps used for the numerical simulations of the BS in this study were acquired at 3T
15 on a Siemens Tim TRIO scanner. Strictly speaking the optimization results are valid only at
16 this field strength and for this scanner type. However, we would expect that this population-
17 based field map gives a good estimate of the susceptibility field distortions introduced by
18 such a scanned object (the volunteer's head and body) in a particular position in a largely-
19 uniform magnetic field. Since the head position and orientation in different MRI scanners are
20 similar (Weiskopf et al., 2006), these optimized parameters can be expected to also hold
21 across different systems to good effect. In addition, the magnitude of these field
22 inhomogeneities would likely scale linearly with the main static magnetic field strength,
23 meaning that even higher BS gains can be expected at higher field strengths. Nonetheless,
24 interaction with the applied shim gradients counteracting the field inhomogeneities mean that

1 this simple relationship is limited making the results dependent on the used hardware, i.e. the
2 type and performance of the shim coils.

3 The large sample of field maps used for optimization this framework promises to provide an
4 improved optimization for group studies, since the typical distribution of field
5 inhomogeneities in the population is better captured compared to previous experimental
6 optimizations based on few volunteers only. In principle, also a subgroup of field maps (e.g. a
7 specific age range or sex) can be used for optimization. However, for studies on atypical
8 populations, e.g. patients with atypical skulls or brains, the field map database and the
9 optimizations based on it may not be optimal. The flexible framework of the proposed
10 method would allow replacing the correct field map database with a patient group specific
11 database or even allow for using individual field maps. This is also valid in case a new field
12 map data base is needed for a different scanner type as discussed above. A description of how
13 to create a new database is given in the methods section of the manuscript (*“Acquisition of a
14 large magnetic field map database”*).

15 In this study field maps with a somewhat lower resolution of 3mm were used. This might be
16 suboptimal for optimizing small structures in a high resolution EPI protocol for a single
17 subject. However, this study aimed to optimize EPI protocols for group studies primarily.
18 Therefore, we can assume that due to inter-subject variability very small structures will be
19 blurred out and do not matter in a group optimization. The optimization for a group and
20 scanning the group with a single fixed parameter set simplifies the experimental workflow
21 significantly and requires only small changes to standard EPI sequences, which facilitates
22 larger population and routine neuroimaging studies.

23 The optimization of BS is only based on the simplified assumption of constant thermal noise.
24 We neither performed an fMRI experiment nor acquired a time series for determining the
25 temporal SNR, which is central for precise measures for sensitivity. Thus, in the vicinity of

1 contrast edges and air–tissue interfaces with strong susceptibility gradients or near large
2 blood vessels, the real BS may turn out to be lower than expected from the simulations, since
3 head motion or respiration and cardiac movement cause prominent physiological noise
4 contributions, especially at high field strength in combination with large voxel sizes (Krueger
5 and Glover, 2001, Krueger et al., 2001, Triantafyllou et al. 2005, Van de Moortele et al.,
6 2008, Hutton et al., 2011). It was however also shown (Triantafyllou et al. 2005) that for the
7 simulations performed here for 3T and $3 \times 3 \times 3 \text{mm}^3$ resolution that thermal noise dominates
8 over physiological noise with a ratio of about 0.89 and 0.70 for $2 \times 2 \times 3 \text{mm}^3$ suggesting that
9 the simplified SNR model for the simulations is still a relatively good approximation in this
10 regime (Balteau et al., 2010). The simplified noise model also prohibits the direct comparison
11 of BS across different spatial resolution, since both thermal SNR and temporal SNR change
12 in this case. However, these effects are not expected to significantly impact comparisons of
13 different parameter sets (slice tilt, z-shim, PE) at the same TE and resolution. Related to this,
14 we note that we did not perform fMRI experiments to validate the predicted BS gain in the
15 different ROIs, since multiple group experiments with different tasks would have been
16 required and going beyond the scope of this study.

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20 **Conclusion**

21 The presented method allows for automated optimization of arbitrary 2D-EPI protocols based
22 on a population magnetic field map database avoiding expensive measurements that consume
23 time and resources. The basic protocol can easily be changed allowing for optimization over a
24 larger parameter space compared to previous experimental based optimization methods. The
25 large dataset of field maps also promises to provide improved optimization for group studies,

1 since the typical distribution of field inhomogeneities in the population is well captured. The
2 results of the optimization by simulations are in good agreement with earlier experimental
3 optimization outcomes (Weiskopf et al., 2006) and the expected BS increases are in line with
4 experimental BS measurements.

5

6 **Acknowledgments**

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9 used in this study. This work is part of the BRAINTRAIN European research network
10 (Collaborative Project) supported by the European Commission under the Health Cooperation
11 Work Programme of the 7th Framework Programme (Grant agreement n° 602186). The
12 Wellcome Centre for Human Neuroimaging is supported by core funding from the Wellcome
13 Trust 091593/Z/10/Z.

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1 Table 1: Optimal parameters for the three principal orientations: transverse (TRA), sagittal
 2 (SAG) and coronal (COR). The basic EPI parameters were: In-plane resolution of $3 \times 3 \text{mm}^2$, a
 3 matrix size of 64×64 and a slice thickness of 3mm. As a measure of generalizability, the
 4 standard deviation for the BS-gain across subjects is listed.

| Region of interest | Z-shim [mT/m*s] | | | Tilt [deg] | | | PE polarity | | | BS-gain [%] | | |
|---------------------------------|--------------------|-----|-----|---------------|-----|-----|-------------|-----|-----|----------------|-------|-------|
| | TRA | SAG | COR | TRA | SAG | COR | TRA | SAG | COR | TRA | SAG | COR |
| mOFC+ rACC | -0.5 | 0.0 | 0.0 | -45 | -45 | 25 | Neg | Neg | Neg | 37±17 | 28±11 | 38±16 |
| Inferior temporal lobes | 0.0 | 0.0 | 0.0 | 45 | 45 | -40 | Neg | Neg | Pos | 12±6 | 15±6 | 4±4 |
| Temporal poles | 1.0 | 0.0 | 0.0 | 45 | 45 | -5 | Neg | Neg | Pos | 44±17 | 27±11 | 0±3 |
| Amygdala | 1.5 | 0.0 | 0.0 | -45 | -45 | 5 | Pos | Pos | Pos | 44±23 | 22±11 | 0±4 |
| Hippocampus+ Parahippocampus | 0.5 | 0.0 | 0.0 | 45 | 45 | -15 | Neg | Neg | Pos | 30±9 | 22±6 | 1±2 |

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1 Table 2: Optimal parameters for transverse orientation for different resolutions and when
 2 using parallel imaging. (I) in-plane resolution of $3 \times 3 \text{mm}^2$, matrix size of 64×64 and slice
 3 thickness of 3mm, (II) in-plane resolution of $2 \times 2 \text{mm}^2$, matrix size of 96×96 and slice
 4 thickness of 2mm and (III) parameters as in (II), using parallel imaging with GRAPPA, factor
 5 2. As a measure of generalizability, the standard deviation for the BS-gain across subjects is
 6 listed.

| Region of interest | Z-shim [mT/m*s] | | | Tilt [deg] | | | PE polarity | | | BS-gain [%] | | |
|-------------------------|--------------------|------|------|---------------|-----|-----|-------------|-----|-----|----------------|-------|-------|
| | I | II | III | I | II | III | I | II | III | I | II | III |
| mOFC+ | -0.5 | -1.0 | -0.5 | -45 | -45 | -45 | Neg | Neg | Neg | 37±17 | 42±20 | 37±18 |
| rACC | | | | | | | | | | | | |
| Inferior temporal lobes | 0.0 | 0.5 | 0.5 | 45 | 45 | 45 | Neg | Neg | Neg | 12±6 | 15±9 | 19±9 |
| Temporal poles | 1.0 | 1.5 | 1.0 | 45 | 45 | 45 | Neg | Neg | Neg | 44±17 | 55±21 | 51±19 |
| Amygdala | 1.5 | 1.5 | 1.5 | -45 | -45 | -45 | Pos | Pos | Pos | 44±23 | 50±25 | 47±21 |
| Hippocampus+ | 0.5 | 0.5 | 0.5 | 45 | 45 | 45 | Neg | Neg | Neg | 30±9 | 42±13 | 39±12 |
| Parahippocampus | | | | | | | | | | | | |

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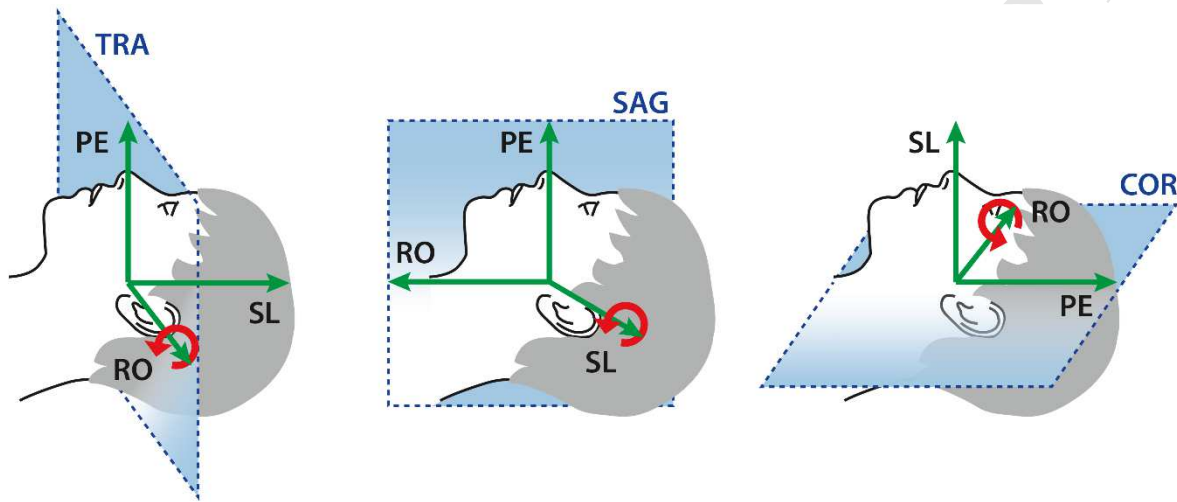
1 Table 3: Comparison of simulation based BS optimization with literature. (a) Results of the
 2 simulation-based optimization in this study and (b) previous optimization using data from
 3 multiple EPI acquisitions (Weiskopf et al., 2006). As a measure of generalizability, the
 4 standard deviation for the BS-gain across subjects is listed.

| Region of interest | Z-shim [mT/m*s] | | Tilt [deg] | | PE polarity | | BS-gain [%] | |
|------------------------------|-----------------|------|------------|-----|-------------|-----|-------------|----|
| | a) | b) | a) | b) | a) | b) | a) | b) |
| mOFC+rACC | -1 | -1.4 | -45 | -45 | Neg | Neg | 20±10 | 19 |
| Inferior temporal lobes | 0 | -0.4 | 30 | 30 | Neg | Neg | 11±4 | 4 |
| Temporal poles | 1 | 0.6 | 45 | 30 | Neg | Neg | 25±10 | 18 |
| Amygdala | 1 | 0.6 | -45 | -45 | Pos | Pos | 23±12 | 13 |
| Hippocampus+Parahippo campus | 1 | 0.6 | 45 | -45 | Neg | Pos | 18±6 | 11 |

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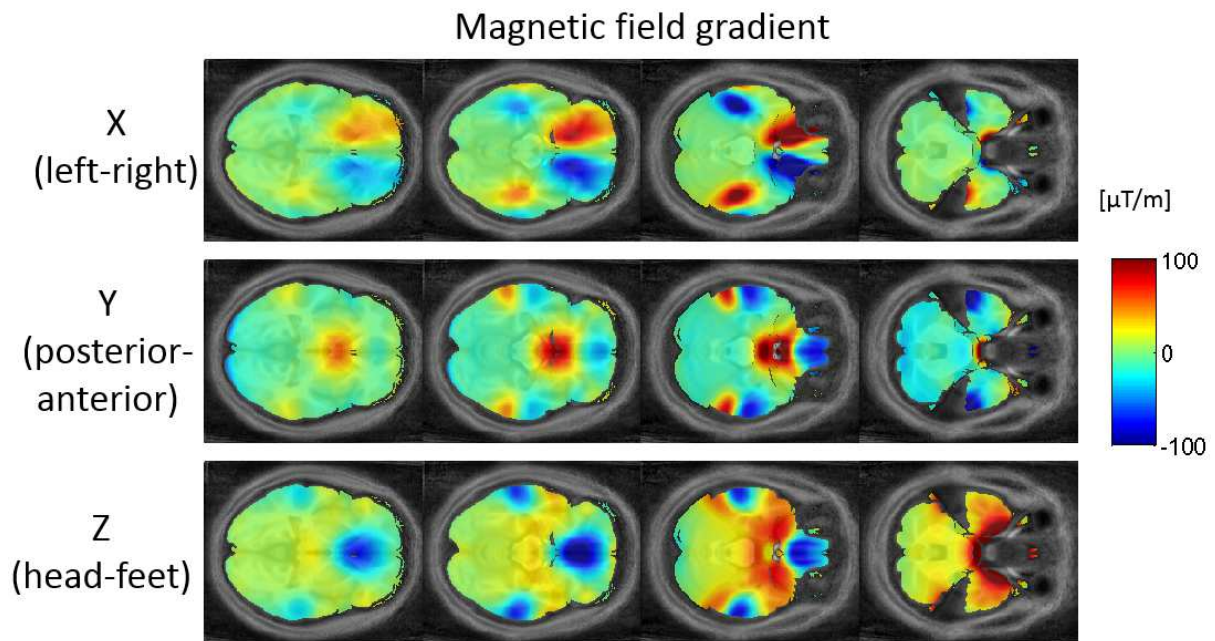
1 Fig 1: Definition of coordinate axis for phase encoding (PE), readout (RO) and slice direction
2 (SL) for the main slice orientations transverse (left), sagittal (middle) and coronal (right) as
3 used in the experiments. For illustration of slice orientations, slices are overlaid over a
4 sagittal view of the human head. The directions for slice angulations and in-plane rotation are
5 denoted with the red arrows respectively.



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1 Fig 2: Maps of susceptibility-induced B_0 field gradients obtained from the field maps for all
2 three directions.

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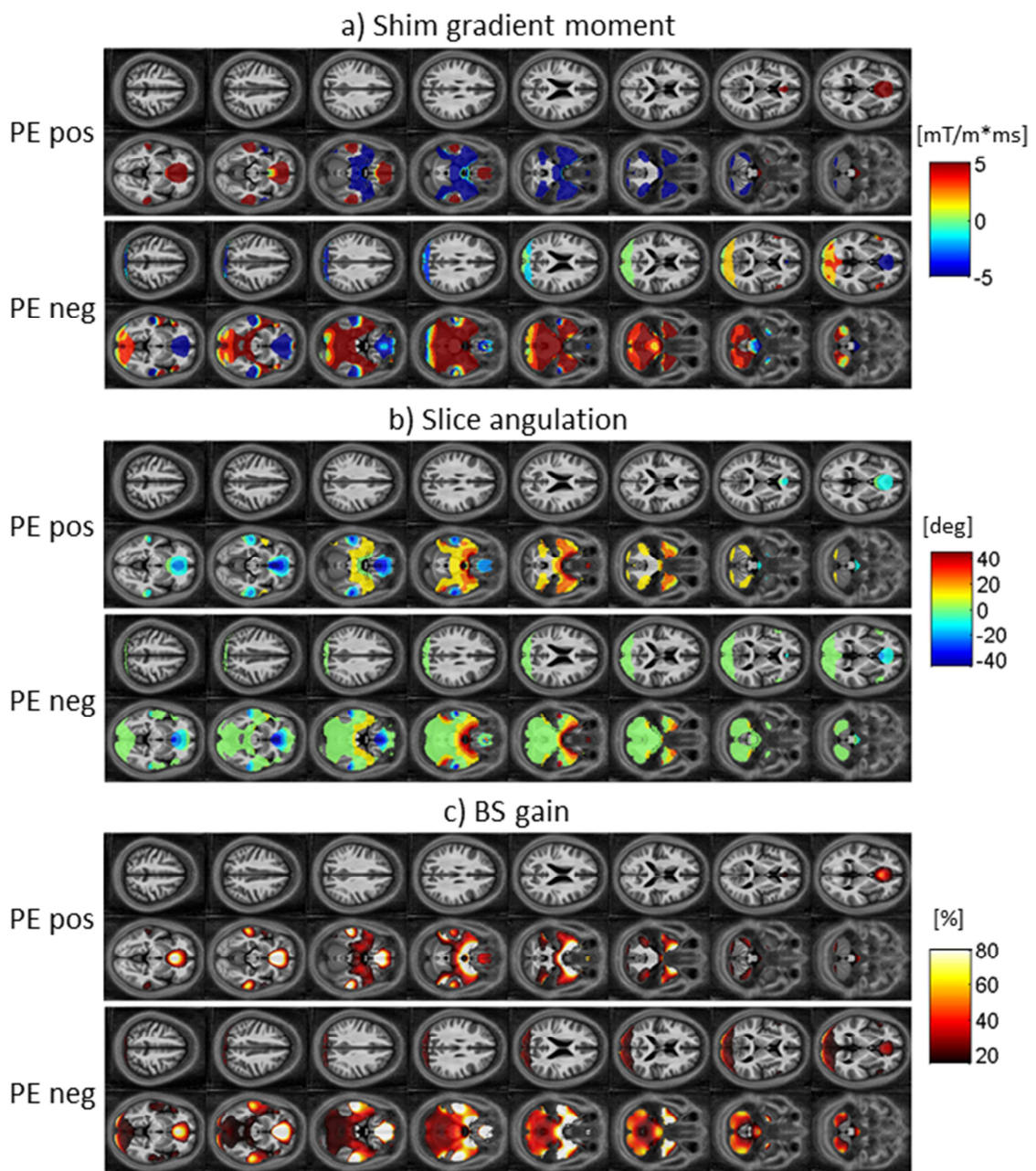


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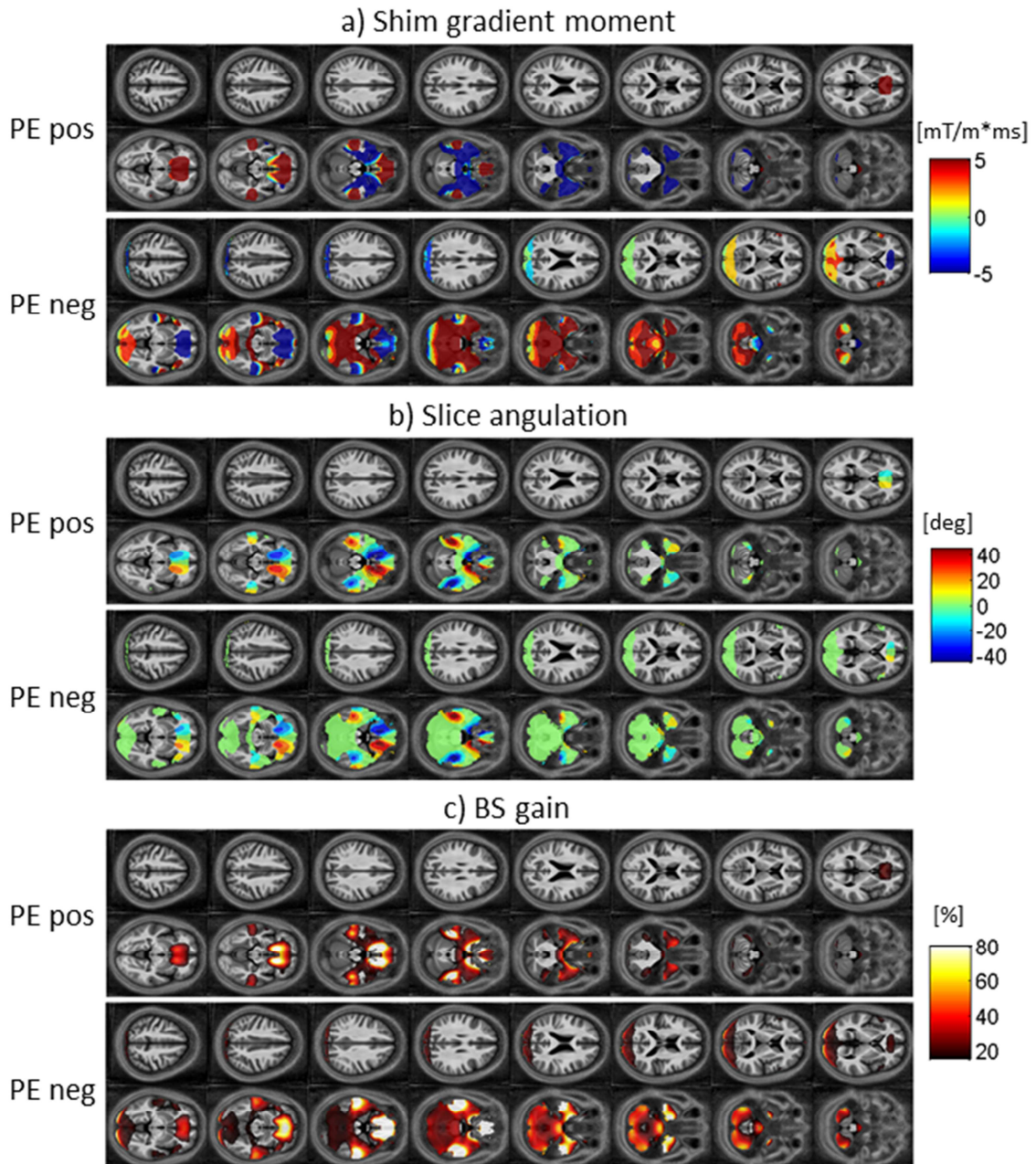
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1 Fig 3: Maps of the voxel-wise optimized parameters for 16 slices in case of oblique
2 transverse acquisitions with an in-plane resolution of $3 \times 3 \text{mm}^2$, a matrix size of 64×64 and a
3 slice thickness of 3mm. Optimal shim gradient moment (a), optimal slice angulation (b) and
4 BS gain achieved with the optimal parameter set compared to standard EPI with no shim
5 gradient and slice angulation (c). In each case the optimized parameters are shown for a
6 positive PE gradient (top row) and for a negative PE gradient (bottom row). A mask has been
7 applied to show only optimized parameters with a BS gain of at least 20%.



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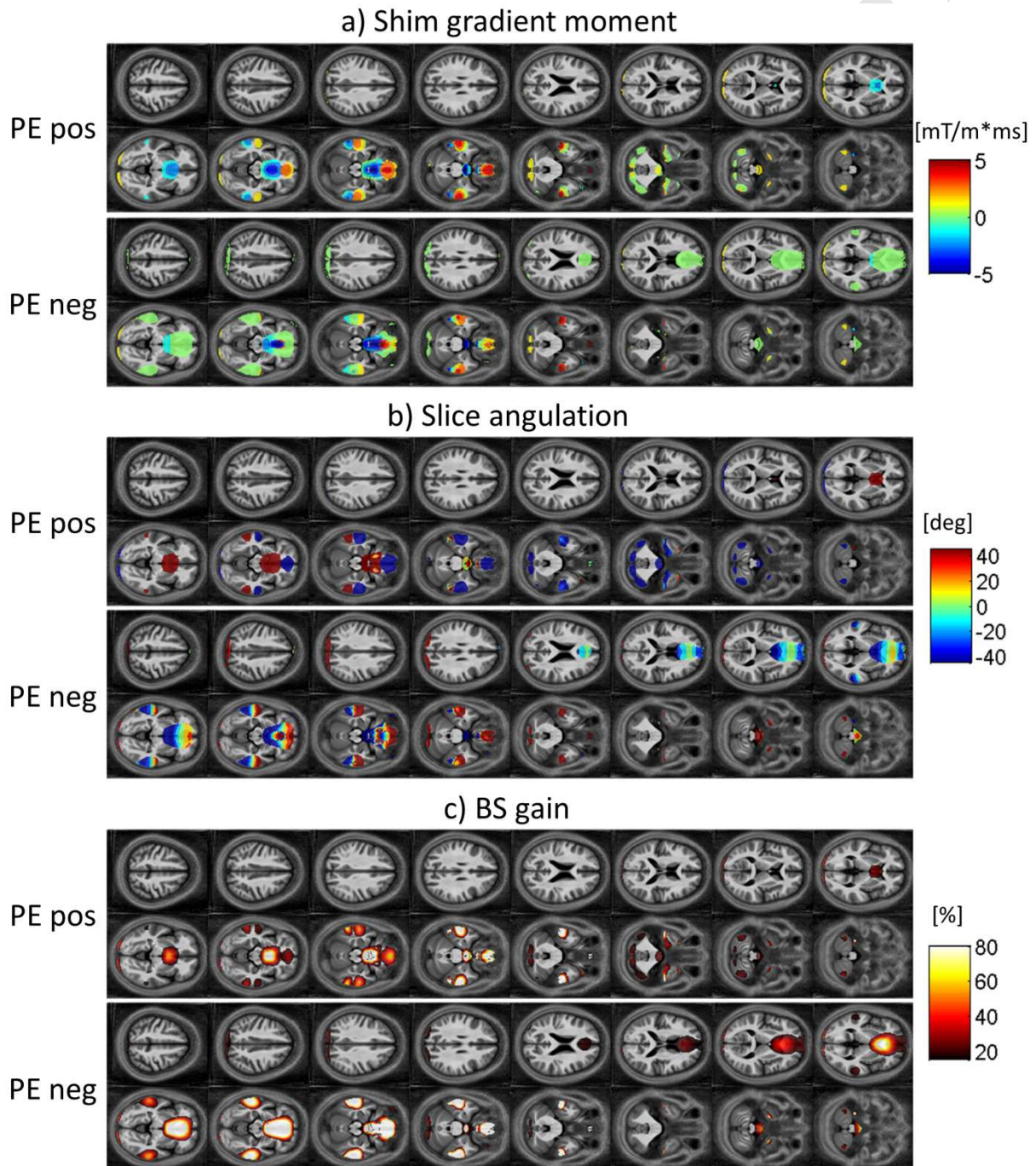
1 Fig 4: Maps of the voxel-wise optimized parameters for 16 slices in case of sagittal
 2 acquisitions. Optimal shim gradient moment (a), optimal in-plane rotation (b) and BS gain
 3 achieved with the optimal parameter set compared to standard EPI with no shim gradient and
 4 slice rotation (c). In each case the optimized parameters are shown for a positive PE gradient
 5 (top row) and for a negative PE gradient (bottom row).



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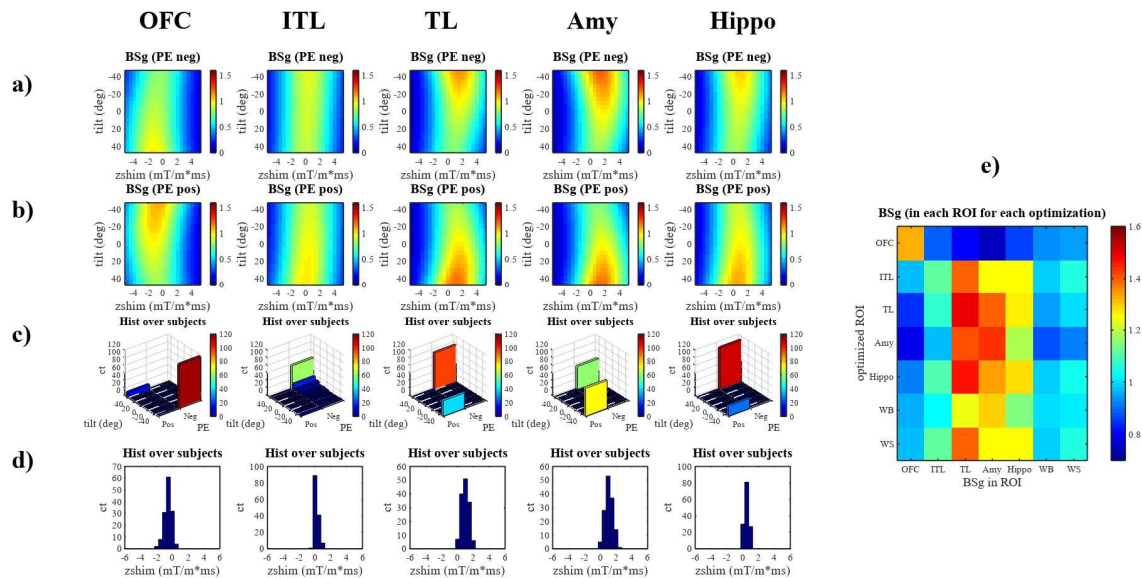
1 Fig 5: Maps of the voxel-wise optimized parameters for 16 slices in case of coronal
2 acquisitions. Optimal shim gradient moment (a), optimal slice angulation (b) and BS gain
3 achieved with the optimal parameter set compared to standard EPI with no shim gradient and
4 rotation (c). In each case the optimized parameters are shown for a positive PE gradient (top
5 row) and for a negative PE gradient (bottom row).



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1 Fig 6: Optimization of the transverse standard resolution protocol for different ROIs: OFC =
 2 mOFC+rACC, ITL = Inferior temporal lobes, TL = Temporal lobes, Amy = Amygdala, and
 3 Hippo = Hippocampus+Parahippocampus. For the optimization based on group-average field
 4 maps the BS gain depending on slice tilt and z-shim assuming either a negative PE direction
 5 (a) or a positive phase encoding direction (b) are shown. To convey how well the optimal
 6 parameters derived from group-average fieldmaps translate to single subjects, the histograms
 7 in (c) and (d) show for how many subjects a particular value of slice tilt and z-shim would
 8 result in the maximal BS gain based on individual field maps.
 9 The number of subjects for the optimal slice tilt are displayed for each PE direction
 10 separately. (e) shows how the optimization for one ROI affects the BS in the other ROIs. As
 11 additional ROIs the Whole Brain (WB) and Well Shimmied areas (WS) are shown.



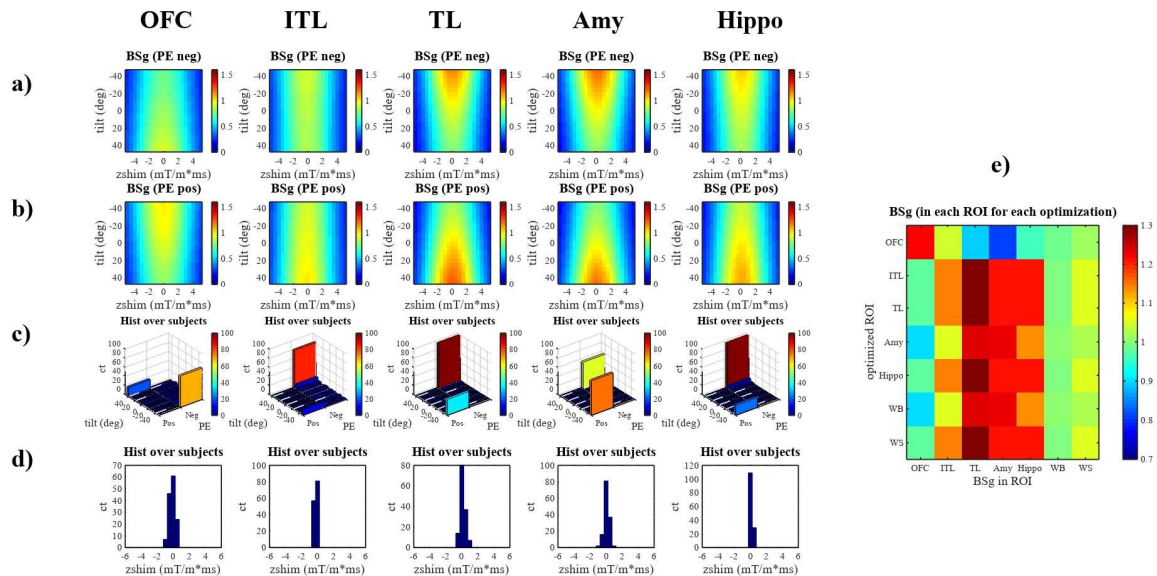
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1 Fig 7: Optimization of the sagittal standard resolution protocol for different ROIs: OFC =
 2 mOFC+rACC, ITL = Inferior temporal lobes, TL = Temporal lobes, Amy = Amygdala, and
 3 Hippo = Hippocampus+Parahippocampus. For the optimization based on group-average field
 4 maps the BS gain depending on slice tilt and z-shim assuming either a negative PE direction
 5 (a) or a positive phase encoding direction (b) are shown. To convey how well the optimal
 6 parameters derived from group-average fieldmaps translate to single subjects, the histograms
 7 in (c) and (d) show for how many subjects a particular value of slice tilt and z-shim would
 8 result in the maximal BS gain based on individual field maps.
 9 The number of subjects for the optimal slice tilt are displayed for each PE direction
 10 separately. (e) shows how the optimization for one ROI affects the BS in the other ROIs. As
 11 additional ROIs the Whole Brain (WB) and Well Shimmied areas (WS) are shown.



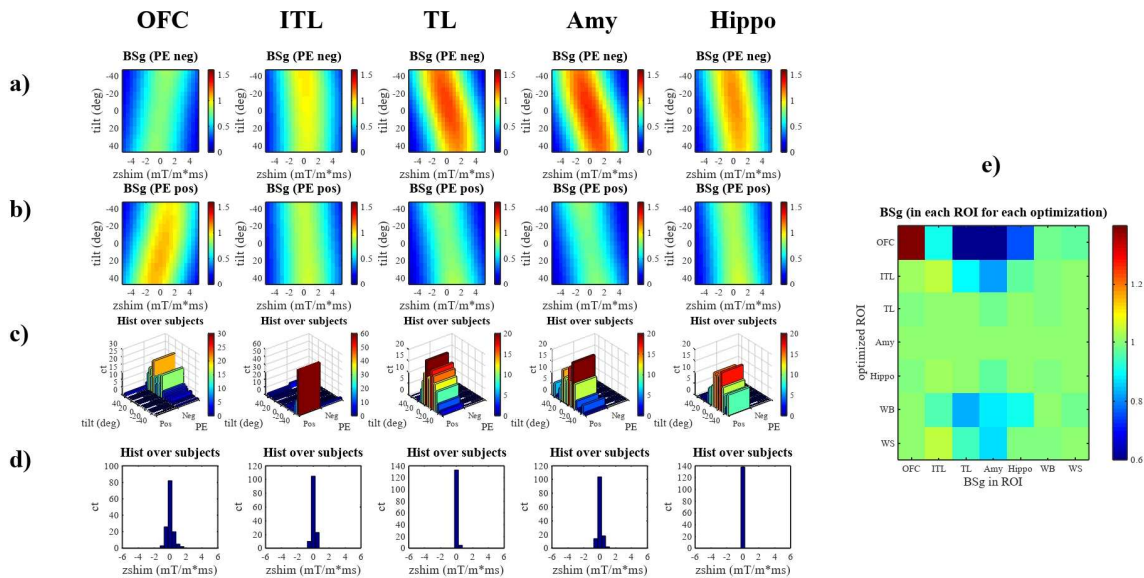
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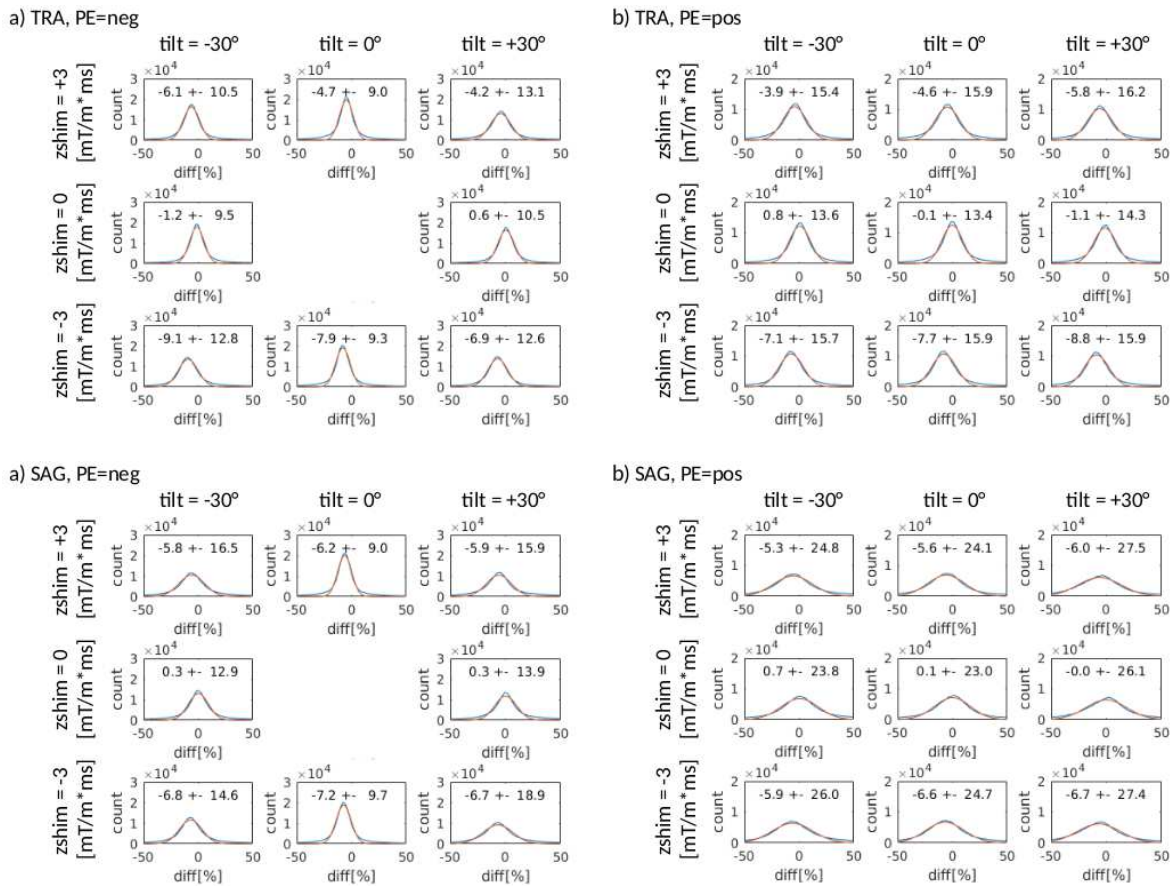
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1 Fig 8: Optimization of the coronal standard resolution protocol for different ROIs: OFC =
 2 mOFC+rACC, ITL = Inferior temporal lobes, TL = Temporal lobes, Amy = Amygdala, and
 3 Hippo = Hippocampus+Parahippocampus. For the optimization based on group-average field
 4 maps the BS gain depending on slice tilt and z-shim assuming either a negative PE direction
 5 (a) or a positive phase encoding direction (b) are shown. To convey how well the optimal
 6 parameters derived from group-average fieldmaps to single subjects, the histograms in (c)
 7 and (d) show for how many subjects a particular value of slice tilt and z-shim would result in
 8 the maximal BS gain based on individual field maps.
 9 The number of subjects for the optimal slice tilt are displayed for each PE direction
 10 separately. (e) shows how the optimization for one ROI affects the BS in the other ROIs. As
 11 additional ROIs the Whole Brain (WB) and Well Shimmied areas (WS) are shown.



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1 Fig 9: Histograms of the percent deviations between simulated and experimentally measured
 2 BS gains pooled across the brain mask (for each of the 36 protocols and six subjects). The
 3 optimization results for the transverse protocol are shown for the negative and positive PE
 4 direction in a) and b), respectively. The optimization results for the sagittal protocol with
 5 negative and positive PE direction are shown in c) and d). The protocol with negative PE and
 6 no tilt and z-shim is not shown, since it was the reference protocol. The blue histogram
 7 represents the experimental data, while the red curve is a Gaussian fit with the respective
 8 estimated mean and standard deviation.



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